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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,806	07/16/2001	Wallace G. Buchholz	FWS-3679	3551

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	8

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/909,806	Applicant(s) BUCHHOLZ ET AL.	
	Examiner Frank W Lu	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *09 July 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on July 9, 2002 has been entered as Paper No:7. The claims pending in this application are claims 1-9 and 20-22. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on July 9, 2002.

Information Disclosure Statement

2. The listing of references in the specification (see pages 8 and 9) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Note that applicant did not address this issue.

Sequence Rules Compliance

3. The sequencing listing submitted on July 9, 2002 still fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Direct the reply to the undersigned.

Drawings

4. The drawing correction for Figure 3 has been approved by the office.

Specification

5. The disclosure is objected to because of the following informalities: There are several nucleic acid sequences in Figure 1. However, these sequences in Figure 1 do not be labeled with SEQ ID Nos.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 22 are rejected as vague and indefinite because it is unclear how different in length each one of the DNA fragments. According to the principal of a sequencing reaction, the length difference between two nucleic acid fragments that are next to each other and are produced by the sequencing reaction is one nucleotide. If size of the nucleotide motif sequence in claims 1 and 21 is more than one nucleotide , claim 1 will not correspond to claim 20 while claim 21 will be correspond to claim 22 wherein claims 20 and 22 appear to indicate that length difference between two nucleic acid fragments that are next to each other and are produced by the

sequencing reaction is more than one nucleotide, which does not fit into the principal of a sequencing reaction. It is also unclear whether each one of the DNA fragments in claims 20 and 22 compares with itself or each one of the DNA fragment in claims 20 and 22 compares with other control DNA that is either shorter or longer than each one of the DNA fragment. Please clarify.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 7-9, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Warburton *et al.*, (Nucleic Acids Res., 20, 6033-6042, 1992).

Regarding claims 1-3, 7, and 9, claim 1 requires a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence wherein the sequence has no inherent secondary structure, claim 2 requires that the dideoxy nucleotide is selected from any kind of dideoxy trinucleotide that can terminate the sequencing reaction wherein the analog is any kind of dideoxy trinucleotide, claim 3 requires that DNA fragments produced by the dideoxy sequencing reaction lack inherent secondary structure, claim 7 requires that DNA template comprises a microsatellite locus, and claim 9 requires that DNA fragment produced by the dideoxy sequencing reaction comprises a respective number of copies of the motif sequence. Warburton *et al.*, teach

PCR amplification of tandemly repeated DNA. By using a novel application of the polymerase chain reaction (repPCR), they amplified a representative sampling of multiple repetitive units from human chromosomes 17 and X and directly sequenced repPCR amplified alpha satellites in the presence of ddNTP (see abstract in page 6033, pages 6034 and 6035, and Figures 1 and 2). Since the sequencing reaction of repPCR amplified alpha satellites included steps of denaturation, annealing, and extension (see page 6035, left column), repPCR amplified alpha satellites became a single stranded DNA after the denaturation. Since it was known that single stranded DNA without a loop structure was no secondary structure, single stranded repPCR amplified alpha satellites after the denaturation was considered as a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence wherein the sequence had no inherent secondary structure as recited in claims 1. Furthermore, there was no evidence to show that single stranded repPCR amplified alpha satellites after the denaturation step in the sequencing reaction had a secondary structure. Since a single stranded repPCR amplified alpha satellite had multiple repetitive units (ie., a 1.9 kb fragment had 16 mer repeat units) (see Figure 1 and page 6035), these multiple repetitive units in the single stranded repPCR amplified alpha satellite were considered as multiple copies of a nucleotide motif sequence as recited in claim 1 wherein these multiple repetitive units were considered as microsatellite locus as recited in claim 7. Since termination of the sequencing reaction was performed in the presence of a 2:1 ratio of each Sequenase ddNTP termination mix to Sequenase extension buffer (see last paragraph of left column and first paragraph of right column in page 6035), a dideoxy sequencing reaction was considered to prepare in the presence of one dideoxy nucleotide terminator as recited in claims 1

and 2. Since the sequencing reaction was performed in the presence of a single primer (see right column in page 6035), DNA fragments produced by the dideoxy sequencing reaction was single stranded with multiple repetitive units (see above). Thus these DNA fragments were considered to lack inherent secondary structure as recited in claim 3 and comprise a respective number of copies of the motif sequence as recited in claim 9. For above reasons, the claims 1-3, 7, and 9 was anticipated by Warburton *et al.*.

Regarding claims 8 and 21, claim 8 requires that the motif sequence comprises a sequence with one unique nucleotide base, and claim 21 requires a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence wherein the sequence has one unique nucleotide base and requires preparing a dideoxy sequencing reaction in the presence of one dideoxy nucleotide terminator corresponding to the unique nucleotide base. Since, as showed above after the denaturation step of the sequencing reaction, a single stranded repPCR amplified alpha satellite had multiple repetitive units (ie., a 1.9 kb fragment had 16 mer repeat units) (see Figure 1 and page 6035), each nucleotide in these multiple repetitive units was considered to be unique to others as recited in claim 8 since these nucleotides occupied different positions in whole DNA sequence. For example, if there was two A in a multiple repetitive unit. the first A was considered to be unique to the second A since the position of the first and second A in whole DNA sequence were different. Since termination of the sequencing reaction was performed in the presence of a 2:1 ratio of each Sequenase ddNTP termination mix to Sequenase extension buffer (see last paragraph of left column and first paragraph of right column in page 6035), each nucleotide in these multiple repetitive units had its own corresponding ddNTP in order to

terminate the sequencing reaction as recited in claim 21. For example, if the first A in a multiple repetitive unit was considered to be unique, its corresponding ddNTP was ddATP in order to terminate the sequencing reaction. For above reasons, the claims 8 and 21 was anticipated by Warburton *et al.*.

Therefore, Warburton *et al.,* teach all limitations recited in claims 1-3, 7-9, and 21.

Response to Arguments

In page 3, fourth paragraph bridging to third paragraph of page 4, applicant argues that Warburton *et al.,* do not "teach or suggest selecting a DNA sequence which has no inherent secondary structure.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, as stated in the rejection, single stranded repPCR amplified alpha satellites after the denaturation step in the sequencing reaction was considered as a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence wherein the sequence had no inherent secondary structure as recited in claims 1 since it was known that single stranded DNA without a loop structure was no secondary structure. Second, there was no evidence to show that single stranded repPCR amplified alpha satellites after the denaturation step in the sequencing reaction taught by Warburton *et al.,* had a secondary structure.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 1-9 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu *et al.,* (US Patent No. 6,197,509 B1, 102(e) date: May 13, 1999) in view of Cocuzza *et al.,* (US Patent No. 5, 484,701, published on January 16, 1996).

Regarding claims 1-4, 7, and 9, claim 1 requires a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence wherein the sequence has no inherent secondary structure, claim 2 requires that the dideoxy nucleotide is selected from any kind of dideoxy trinucleotide that can terminate the sequencing reaction wherein the analog is any kind of dideoxy trinucleotide, claim 3 requires that DNA fragments produced by the dideoxy sequencing reaction lacks inherent secondary structure, claim 4 requires that the motif sequence is 2-6 nucleotide, claims 5 and 6 require copy numbers of the motif sequence are from 10 to 200, claim 7 requires that DNA template comprises a microsatellite locus, and claim 9 requires that DNA fragment produced by the dideoxy sequencing reaction comprises a respective number of copies of the motif sequence. Xu et al., teach a method of analyzing DNA using contiguous repeats. As shown in Example 1, a cosmid containing human inducible nitric oxide synthase gene coding region and its promoter region was shot-gun cloned with Pst I and Hind III restriction enzymes into a pBluescript SK vector. Subclones were then sequenced using an ABI automatic sequencer with M13 universal and reverse primers. One of the Pst I subclones was shown to contain 11 perfect contiguous pentanucleotide repeats (CCTTT/GGAAA) (see column 3 and Figures 1A

and 1B). Note that: (1) although Xu et al., did not directly disclose steps of a sequencing reaction including denaturation, annealing, and extension, it was obvious to one having ordinary skill in the art at the time the invention was made to have performed these method steps during the process of DNA sequencing since it was known that sequencing a double stranded DNA must include steps of denaturation, annealing, and extension. This was supported by Cocuzza *et al.,* wherein they boiled M13mp 18 DNA for 2 min (for detail, see column 12, lines 1-24). Since it was known that single stranded DNA without a loop structure was no secondary structure and the Pst I subclone containing 11 perfect contiguous pentanucleotide repeats (CCTTT/GGAAA) became a single stranded DNA after the denaturation step, in view of patents of Xu *et al.,* and Cocuzza *et al.,* single stranded Pst I subclone after the denaturation was considered as a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence without an inherent secondary structure as recited in claims 1 wherein 11 perfect contiguous pentanucleotide repeats (CCTTT/GGAAA) was considered as multiple copies (ie., n=11) of a nucleotide motif sequence as recited in claims 1 and 4-6 and was considered as microsatellite loci as recited in claim 7. Furthermore, there was no evidence to show that single stranded Pst I subclone after the denaturation step in the sequencing reaction taught by Xu *et al.,* had an inherent secondary structure; (2) although Xu et al., did not directly disclose to perform a sequencing reaction in the presence of a dideoxy nucleotide terminator as recited in claims 1 and 2, it was obvious to one having ordinary skill in the art at the time the invention was made to have performed a DNA sequencing reaction in the presence of at least one dideoxy nucleotide terminator since it was known that the dideoxy nucleotide terminator was critical component in a sequencing reaction in

order to stop the sequencing reaction. This was supported by Cocuzza *et al.,* wherein they used ddCTP as a dideoxy nucleotide terminator (for detail, see column 12, lines 1-24); (3) although Xu et al., did not directly disclose to perform a sequencing reaction in the presence of a single primer, it was obvious to one having ordinary skill in the art at the time the invention was made to have performed a DNA sequencing reaction in the presence of a single primer, since it was known that a sequencing reaction was performed using a single primer. This was supported by Cocuzza *et al.,* wherein they used a biotin labeled single primer for a sequencing reaction (for detail, see column 12, lines 1-24). Since the sequencing reaction was performed in the presence of a single primer, DNA fragments produced by the dideoxy sequencing reaction was single stranded with multiple repetitive units (see above). Thus these DNA fragments were considered to lack inherent secondary structure as recited in claim 3 and comprising a respective number of copies of the motif sequence as recited in claim 9.

Regarding claims 8 and 21, claim 8 requires that the motif sequence comprises a sequence with one unique nucleotide base, and claim 21 requires a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence wherein the sequence has one unique nucleotide base and requires preparing a dideoxy sequencing reaction in the presence of one dideoxy nucleotide terminator corresponding to the unique nucleotide base. Since, as showed above, after the denaturation step of the sequencing reaction, a single stranded Pst I subclone had 11 perfect contiguous pentanucleotide repeats (CCTTT/GGAAA) (see above), each nucleotide in these multiple repetitive units was considered to be unique to others as recited in claim 8 since these nucleotides occupied different positions in whole DNA sequence. For example, the first C

in a perfect contiguous pentanucleotide repeat (CCTTT/GGAAA) was considered to be unique to the second C in the same repeat since the position of the first and second C in whole DNA sequence are different. If the first C in the repeat was considered to be unique, its correspond ddNTP was ddCTP in order to terminate the sequencing reaction.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have used a single stranded DNA having a sequence comprising multiple copies of a nucleotide motif sequence having one unique nucleotide base without an inherent second structure as a template for a DNA sequencing reaction in the presence of a dideoxy nucleotide terminator in view of the patents of Xu *et al.,* and Cocuzza *et al.*. One having ordinary skill in the art would have been motivated to do so because it was known that a sequencing reaction of a double stranded DNA must include a denaturation step and must be performed in the presence of at least one dideoxy nucleotide terminator. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to use a single stranded DNA from a denatured double stranded DNA as a template to perform a sequencing reaction in the presence of at least one dideoxy nucleotide terminator.

Response to Arguments

In page 5, second paragraph to fourth paragraph of applicant's remarks, applicant argues that: Xu *et al.,* "fail to teach or suggest selecting a DNA sequence which has no inherent secondary structure.". and "fail to disclose any motif any DNA sequence comprising multiple copies of a motif sequence with one unique nucleotide base.".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, as stated in the rejection, since it was known that single stranded DNA without a loop structure was no secondary structure and the Pst I subclone containing 11 perfect contiguous pentanucleotide repeats (CCTTT/GGAAA) became a single stranded DNA after the denaturation step, in view of patents of Xu *et al.,* and Cocuzza *et al.,* single stranded Pst I subclone after the denaturation was considered as a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence without an inherent secondary structure as recited in claim 1. Second, there was no evidence to show that single stranded Pst I subclone after the denaturation step in the sequencing reaction taught by Xu *et al.,* had an inherent secondary structure. Third, since, after the denaturation step of the sequencing reaction, a single stranded Pst I subclone had 11 perfect contiguous pentanucleotide repeats (CCTTT/GGAAA) (see above), each nucleotide in these multiple repetitive units was considered to be unique to others as recited in claim 8 since these nucleotides occupied different positions in whole DNA sequence. For example, the first C in a perfect contiguous pentanucleotide repeat (CCTTT/GGAAA) was considered to be unique to the second C in the same repeat since the position of the first and second C in whole DNA sequence are different. If the first C in the repeat was considered to be unique, its correspond ddNTP was ddCTP in order to terminate the sequencing reaction.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. No claim is allowed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
March 5, 2003

Ethan Whisenant, Ph.D.
Primary Examiner
Art Unit 1634